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EXAMINER	
BUGAISKY, GABRIELE E	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/441,654	CHAN, SHAM-YUEN	
	Examiner	Art Unit	
	Gabriele E. BUGAISKY	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,6-9,15,18-21,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,6-9,15,18-21,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0903* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/19/2003 has been entered.

Specification

The objection to the specification is withdrawn, based upon the amendment.

Information Disclosure Statement

The references that have been crossed out of the PTO-1449 submitted 9/2003 are already of record. A reference can only be considered once.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. The claims specify the specific linkages of the sialic residues. It is noted that the specification states on page 4:

"The glycosylated bikunin produced from the mammalian cells is preferably capped with sialic acids having alpha-(2, 3) and a1pha-(2,6) linkages. ln a less preferred embodiment, the glycosylation includes sialic acids with only a1pha-(2-3) linkages."

The specification, however, does not describe how to determine the specific linkage, nor does it describe which mammalian cells are expected to produce the recited linkages. Further, it does not describe, e.g., how to obtain, as specified in claim 8, a bikunin which

"comprises at least one sialic acid residue bonded within the glycosylated bikunin via an alpha-(2,3) linkage and at least one sialic acid residue bonded within the glycosylated bikunin via an a1pha-(2,6) linkage."

In that respect, the specification does not describe how one may determine that all molecules have both linkages, vs. a bikunin preparation in which half the molecules have a1pha-(2,6) linkages, and the other half have alpha-(2,3) linkage.

Claims 6-8 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As stated above, the specification does not describe how to obtain the specific linkages recited by the claims. Which is not described cannot be considered enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

Claims 2, 6-9 and 25 remain rejected under 35 U.S.C. 102(b) as being anticipated by Shimomura *et al.* (US patent 5731412) Shimomura *et al.* provides for purification of human hepatocyte growth factor activator inhibitor type 2 from conditioned medium of MKN45 cells; the primary amino acid sequence of human hepatocyte growth factor activator inhibitor type 2 is identical to the mature bikunin of instant SEQ ID NO:1 and thus has the identity of placental bikunin. The reference is deemed anticipatory for the claimed subject matter because the protein is obtained from both human MKN45 cells and COS cells (see Example 8) The glycosylation pattern is an intrinsic property of the cells which produce the protein. Since mammalian cells add sialic acid residues to their glycoproteins, it is presumed that the protein of Shimomura *et al* has the recited linkages of the instant claims . Applicant's arguments filed 9/19/2003 have been fully considered but they are not persuasive. It is stated that

> the examiner has not provided "a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art," as required under Levy (*Ex parte Levy*, 17 USPQZd 1461, 1464 (Bd. Pat. App. &Inter. 1990).

As stated above, the specification does not describe how to determine the specific linkages, nor does it describe which mammalian cells are expected to produce the recited linkages. It states on page 6 that "mammalian cells produce proteins having sugar chains capped with sialic (neuraminic) acid residues". It also states on p. 11 "Preferred cultured mammalian cells include the COS-I (ATCC No. CRL 165%, COS-7 (ATCC No. CRL 1651), BHK. . . " Absent evidence to the contrary, the Examiner presumes that the preferred cell types produce the desired linkages.

As far as the Examiner can determine, the sialic acid content of the recombinantly produced protein is not intrinsic to the recombinant protein, but is instead a feature of the cell line used to produce the bikunin or monokunin. Thus, the process of making the protein in mammalian cells is what determines the specific sialic acid content Although the instant claims specify sialic acid linkages, these linkages are a feature of the process used to produce the protein, and thus the Examiner reads these claims as product by process.

A product claimed by process is unpatentable if it is the same as, or obvious from, that product which was previously known to be made by another method (*In re Thorpe,* 227 USPQ 964, CAFC 1985).

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658

(Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) There, claims were directed to a titanium alloy containing 0.2-0.4% Mo and 0.6-0.9% Ni having corrosion resistance. A Russian article disclosed a titanium alloy containing 0.25% Mo and 0.75% Ni but was silent as to corrosion resistance. The Federal Circuit held that the claim was anticipated because the percentages of Mo and Ni were squarely within the claimed ranges. The court went on to say that it was immaterial what properties the alloys had or who discovered the properties because the composition is the same and thus must necessarily exhibit the properties.).

Because it is perhaps more similar in fact pattern, attention is drawn to *Ex parte Gray*, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989). The prior art disclosed human nerve growth factor (β-NGF) isolated from human placental tissue. The claim was directed to β-NGF produced through genetic engineering techniques. The factor produced seemed to be substantially the same whether isolated from tissue or produced through genetic engineering. While the applicant questioned the purity of the prior art factor, no concrete evidence of an unobvious difference was presented. The Board stated that the dispositive issue is whether the claimed factor exhibits any unexpected properties compared with the factor disclosed by the prior art. The Board further stated that the applicant should have made some comparison between the two factors to establish unexpected properties since the materials appeared to be identical or only slightly different.).

The Examiner maintains that the glycosylated hepatocyte growth factor activator inhibitor type 2 of Shimomura made by COS cells and human MKN45 cells appears to be the same as the instantly claimed protein.

Claims 2, 6-9, 15, 18-20 and 25-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Tamburini et al.(U.S. Patent No. 6583108.).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 2, 6-9, 15, 18-20 and 25-26 directed to an invention not patentably distinct from claims of commonly assigned 6583108. Specifically,. The patent claims glycosylated proteins and does not specify the sialic acid linkages; however, as discussed above, the carbohydrate moiety of the protein produced by the mammalian cells is inherent to each cell type.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned 6583108, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the

assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 6-9 15, 18-21 and 25-26 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tamburini *et al.* (WO 97/33996-refernce #29) The reference provides for not only for cloned human placental bikunin and monokunin expressed in *Saccharomyces* and Sf-9 cells , but also native human bikunin purified from placenta (example 7), which is glycosylated and inherently contains sialic acid; it further teaches on page 36, lines 8-11:

> A variety of combinations of expression vector and host organism exist which can be used for the production of the placental bikunin variants. Suitable host cells include

baculovirus infected Sf9 insect cells, mammalian cells such as BHK, CHO, Hela and C-127, bacteria such as E. coli, and yeasts such as Saccharomyces cervisiae.

It further states on that page, lines 23-25:

> Use of mammalian and yeast systems are most preferred for the expression of larger placental bikunin variants containing both inhibitor domains such as the variant bikunin (7-159)

Barring absence to the contrary, the purified human bikunin is presumed to possess the recited sialic acid linkages, and thus anticipates the claimed invention. Alternatively, one of skill in the art has sufficient teaching and motivation to use any of the recited cell lines that would make the appropriate linkages, with a reasonable expectation of success..

Claims 15,18-21 and 26 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Shimomura et al. in view of Delaria *et al.* Shimomura *et al.*. is discussed above. They do not test the activity of each Kunitz domain against human hepatocyte growth factor activator. Delaria *et al.*. provide monokunins produced in Sf-1 cells and tests their activity against the factor VIIa-tissue factor complex and factor Xa, but does not test it against human hepatocyte growth factor activator. It would have been obvious for one of skill in the art at the time of the invention to produce the single Kunitz domains of Delaria *et al* in the COS culture system of Shimomura et al., with the intended use for testing each glycosylated domain for activity against human hepatocyte growth factor activator. One would have had a very high expectation of success in the venture. Applicant is directed to the above discussion regarding glycosylation in mammalian cells.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2, 6-9, 15, 18-20 and 25-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 and 4-5 of U.S. Patent No. 6583108. Although the conflicting claims are not identical, they are not patentably distinct from each other because the independent claims of the patent specify bikunin or monokunin and dependent claim 4 specifies glycosylation. The patent provides for not only for cloned human placental bikunin and monokunin, but also native human bikunin purified from placenta (example 7), which is glycosylated and inherently contains sialic acid; it further teaches in column 29, lines 1-7:

> A variety of combinations of expression vector and host organism exist which can be used for the production of the placental bikunin variants. Suitable host cells include baculovirus infected Sf9 insect cells, mammalian cells such as BHK, CHO, Hela and C-127, bacteria such as E. coli, and yeasts such as Saccharomyces cervisiae.

It further states in column 29, lines 20-23:

Use of mammalian and yeast systems are most preferred for the expression of larger placental bikunin variants containing both inhibitor domains such as the variant bikunin (7-159)

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gabriele E. BUGAISKY whose telephone number is (571) 272-0945. The examiner can normally be reached on Tues.- Fri 8:15 AM-1:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher SF Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-0700.

Gabriele E. BUGAISKY
Primary Examiner
Art Unit 1653